Original Studies

Right Ventricular Remodelling after Transcatheter Pulmonary Valve Implantation: Time Matters!

Efstathios D. Pagourelias,[1] MD, PhD, Ana M Daraban,[1] MD, Razvan O Mada,[1] MD, Jürgen Duchenne,[1] MSc, Oana Mirea,[1] MD, PhD, Bjorn Cools,[2] MD, PhD, Ruth Heying,[2] MD, PhD, Derize Boshoff,[2] MD, PhD, Jan Bogaert,[3] MD, PhD, Werner Budts,[1] MD, PhD, Marc Gewillig,[2] MD, PhD, and Jens-Uwe Voigt,[1*] MD, PhD

Objectives: To define the optimal timing for percutaneous pulmonary valve implantation (PPVI) in patients with severe pulmonary regurgitation (PR) after Fallot's Tetralogy (ToF) correction. **Background:** PPVI among the aforementioned patients is mainly driven by symptoms or by severe right ventricular (RV) dilatation/dysfunction. The optimal timing for PPVI is still disputed. **Methods:** Twenty patients [age 13.9 ± 9.2 years, (range 4.3–44.9), male 70%] with severe PR (≥3 grade) secondary to previous correction of ToF, underwent Melody valve (Medtronic, Minneapolis, MN) implantation, after a pre-stent placement. Full echocardiographic assessment (traditional and deformation analysis) and cardiovascular magnetic resonance evaluation were performed before and at 3 months after the intervention. 'Favorable remodelling' was considered the upper quartile of RV size decrease (>20% in 3 months). **Results:** After PPVI, indexed RV effective stroke volume increased from 38.4 ± 9.5 to 51.4 ± 10.7 mL/m^2, ($P = 0.005$), while RV end-diastolic volume and strain indices decreased (123.1 ± 24.1–101.5 ± 18.3 mL/m^2, $P = 0.005$ and −23.5 ± 2.5 to −21 ± 2.5%, $P = 0.002$, respectively). After inserting pre-PPVI clinical, RV volumetric and deformation parameters in a multiple regression model, only time after last surgical correction causing PR remained as significant regressor of RV remodelling [$R^2 = 0.60$, beta = 0.387, 95%CI(0.07–0.7), $P = 0.019$]. Volume reduction and functional improvement were more pronounced in patients treated with PPVI earlier than 7 years after last RV outflow tract (RVOT) correction, reaching close-to-normal values. **Conclusions:** Early PPVI (<7 years after last RVOT operation) is associated with a more favorable RV reverse remodelling toward normal range and should be considered, before symptoms or RV damage become apparent.

Key words: transcatheter valve implantation; right ventricular function; imaging TEE/TTE; imaging cardiac magnetic resonance imaging; congenital heart disease adults

[1]Department of Cardiovascular Diseases, University Hospital Leuven, Leuven, 3000, Belgium
[2]Department of Pediatric Cardiology, University Hospital Leuven, Leuven, 3000, Belgium
[3]Department of Radiology, University Hospital Leuven, Leuven, 3000, Belgium

Conflict of interest: The authors report no relationships that could be construed as a conflict of interest.

*Correspondence to: Prof. Dr. med. Jens-Uwe Voigt; Department of Cardiovascular Diseases, University Hospital Gasthuisberg, Herestraat 49, 3000 Leuven, Belgium. E-mail: jens-uwe.voigt@uzleuven.be

Received 12 June 2016; Revision accepted 16 January 2017

DOI: 10.1002/ccd.26966
Published online 00 Month 2017 in Wiley Online Library (wileyonlinelibrary.com)

INTRODUCTION

Surgical correction of Fallot's Tetralogy (ToF) either by transannular patching or even limited infundibulotomy, typically leads to chronic pulmonary regurgitation (PR) [1]. PR is then associated with late adverse events such as aneurysmal dilatation of the right ventricular outflow tract (RVOT), right ventricular (RV) dysfunction, progressive tricuspid valve regurgitation (TR), exercise intolerance, arrhythmias, and eventually premature sudden death [2–4]. Efforts to mitigate these outcomes have focused on restoration of normal pulmonary valve (PV) function with traditional methods of pulmonary valve replacement being surgical. The introduction and refinement, however, of percutaneous pulmonary valve implantation (PPVI) during the last years, has led to an improved safety and feasibility of the intervention as well as to more satisfactory short and long term results with regard to RV and PV function and structure [5–11].

Despite the technical success, the low complication rate and the marked improvement in RV hemodynamics following PPVI, the optimal timing for PV replacement among ToF patients with PR still remains a subject of debate [9]. Current guidelines suggest an intervention for PR in a "later time point" when the patient is symptomatic or severe RV dilatation/dysfunction is present [9]. This "watchful" waiting, however, may truly jeopardise RV functional and structural recovery following PPVI. Based mostly on data coming from ToF patients, previous studies have suggested that chronic exposure to pulmonary incompetence may increase RV fibrosis burden and concomitant RV dysfunction, which may then prevent sufficient functional and structural recovery after PPVI and lead to increased late mortality due to mechanical failure or arrhythmias [2–4,12]. Therefore identifying the impact of PPVI timing on myocardial recovery would help to clarify if in this situation "the earlier is the better."

Although an increasing number of publications have focused on the clinical and hemodynamic outcomes after PPVI in variable substrates of PV pathologies among CHD patients (including ToF) [8,10,11,13], scarce data exist regarding RV function alterations among patients with pure chronic PR undergoing PPVI (assessed also with deformation analysis). Additionally, the impact of the time of PPVI on RV structure and function has not thoroughly been investigated. Therefore, the aims of this study were: (1) to determine global and segmental RV and left ventricular (LV) structure and function alterations following PPVI in patients with pure PR secondary to correction of a rather uniform CHD substrate and (2) to explore the impact of the timing of the PV replacement procedure on the structural and functional recovery of the myocardium.

METHODS

Patients

Patients were recruited from September 2012 till January 2015 from the outpatient clinic of the department of Pediatric Cardiology, where they are routinely seen for annual evaluation. Main inclusion criteria for PPVI in this ongoing, prospective study was severe PR ($\geq$ grade 3) accompanied by symptoms (mainly dyspnea and limited exercise capacity or inability to follow everyday activities especially for children) or concomitant structural disorders [as assessed by echocardiography, cardiovascular magnetic resonance (CMR) or both]: PR regurgitant fraction $\geq$25% or RV/LV end diastolic volume ratio (RVEDV/LVEDV) $>$2 or RV ejection fraction (EF) $<$47% or LVEF $<$55% or sustained tachyarrhythmia related to right heart volume overload [13]. Exclusion criteria for this study were: (1) The co-existence of pulmonic stenosis with a maximum gradient $>$ 30 mm Hg, (2) serial or other surgical or interventional procedures between Tof correction and PPVI, and (3) RVOT diameter $<$18 or $>$21 mm due to outer diameter of the valve of 24 mm. Due to national reimbursement regulations, the Melody valve (Medtronic, Minneapolis, MN) was exclusively used. Informed consent was obtained from each patient or the parents. The study protocol fully conformed to the ethical guidelines of the 1975 Declaration of Helsinki, as reflected in a prior approval by our institution's human research committee

PPVI Procedure

All procedures were performed under the same general anesthesia protocol. Anesthesia was induced with mask administration of high concentrations of sevoflurane until tracheal intubation. Anesthesia was then maintained with a combination of propofol (125–300 mcg/kg/min) and remifentanil (0.25 mcg/kg/min) infusion throughout the whole procedure. None of the patients received catecholamines or other inotropic substances during or after the procedure.

Both pre-stenting and PPVI follow similar steps and have been described extensively elsewhere [5,11,13]. Briefly, the vascular access was obtained from either the femoral vein or the internal jugular vein. A standard right heart catheterization for hemodynamic measurements was performed at the beginning and end of the intervention.

The pre-stenting procedure started with a balloon-interrogation of the RVOT to delineate the potential zone of retention for the stent. Simultaneous coronary angiography was performed in all patients to ensure absence of coronary compression. Subsequently, a bare hybrid open cell [AndraStent®, AndraMed, GmbH, Reutlingen, Germany] was deployed on a Balloon in Balloon dilatation catheter

(NuMED, Hopkinton, NY) using hand inflation. PPVI was scheduled 2 months after stent implantation, to allow endothelial tissue ingrowth to fix the stent to the heart and vessel wall before the valve implantation. The PPVI procedure started with an angiography of the RV outflow and pulmonary artery to determine the optimal site for valve deployment. A bovine valve on a covered stent (Melody valve) was then deployed within the pre-stent using a balloon inflated to its full dimension. The delivery system was then removed and angiography and hemodynamic measurements were repeated.

Transthoracic Echocardiography

Image acquisition protocol. All patients were examined using a commercially available Vivid E9 scanner (GE Healthcare, Horten, Norway) equipped with an M5S-D (2D) transducer. Loops of at least three cardiac cycles were acquired and stored digitally for later offline analysis on an EchoPAC workstation (version BT12, GE Vingmed Ultrasound, Horten, Norway). Frame rate used for image acquisition was >60 fps in all patients included and for all echocardiographic exams.

Echocardiographic assessment of the enrolled patients was performed at 3 time points: (1) ECHO 1: afternoon before the pre-stent procedure; (2) ECHO 2: morning after the PPVI procedure, before patient's discharge; (3) ECHO 3: 3 months follow-up.

Standard morphological and Doppler echocardiography analysis. At end-diastole, we obtained the RV basal width at the tips of the tricuspid valve leaflets (RVD1), the mid-cavitary width (RVD2), the long axis (RVD3) and the area (RV EDA). The latter was also measured at end-systole (RV ESA) and fractional area change (FAC) was derived as follows:

$$(\text{RV EDA} - \text{RV ESA})/\text{RV EDA}.$$

The tricuspid annular plane systolic excursion (TAPSE) was measured from anatomical M mode tracings [14]. Right atrial area (RA) was measured in the apical 4-chamber view at end-systole [14]. All parameters above presented are indexed to body surface area (BSA) [15]. LV internal dimensions were measured and LVEF was calculated according to the biplane Simpson's method [14]. The maximum instantaneous RVOT gradient (MIG RVOT) was measured by CW-Doppler. Significant outflow tract obstruction was defined as MIG-RVOT > 30 mm Hg. The severity of PR was classified based on regurgitant jet width relative to the annulus, the characteristics of the CW Doppler envelope and the detectable origin of the retrograde diastolic flow in the pulmonary artery [16,17]. More specifically PR was scored: 0, none; 1, trivial (jet width ≤1/3 of the pulmonary valve annulus); 2, mild (≥1/3 but ≤1/2 of the pulmonary valve annulus); 3, moderate (≥1/2 but less than the pulmonary valve annulus and regurgitation beginning in the pulmonary trunk), or 4, severe insufficiency (jet width equal to the pulmonary valve annulus with regurgitation seen in the branch pulmonary arteries) [16,17]. On mitral and tricuspid valve we measured parameters of diastolic function as previously indicated [14,16–19].

Two-dimensional speckle-tracking deformation analysis. RV global longitudinal peak systolic strain (RV-GLS) was derived from 2D Speckle tracking of the entire RV contour in the apical 4 chamber view [20]. Tracking results were carefully inspected. If needed, manual correction was applied. RV-GLS was not calculated if more than 1 RV segments had to be excluded from analysis (none of the study patients fulfilled this condition). PW-Doppler recordings of the PV, were used to define RV end-systolic events including strain. A similar procedure was applied for LV, using the 3 apical views and an 18-segment model of the ventricle. End systole for LV was defined by the aortic valve closure.

Beginning of heart cycle was set at the beginning of QRS and time to peak longitudinal strain was measured from there till the peak systolic strain value. The times were then corrected for heart rate using the Bazett's formula (Time interval/$\sqrt{}$RR in sec) [21].

CMR Analysis

All CMR studies were performed on a 1.5T Philips Intera-CV (Philips, Best, The Netherlands) using dedicated cardiac software (Philips Intera-CV workstation), phased-array surface receiver coil and ECG triggering. All enrolled patients had CMR either before the initial RVOT stenting and/or 3 months after PPVI, however, only data from patients with paired CMR acquisitions (before and 3 months after PPVI) were used for this analysis. Breath-hold cine imaging, using the steady-state free-precession sequence was performed. In the cardiac short-axis, the left ventricle was completely encompassed using a 8-mm slice thickness and 2-mm interslice gap. To better delineate and measure RV volumes steady-state free-precession sequence axial images were also acquired. Velocity-encoded phase-contrast magnetic resonance imaging was utilized to quantify regurgitant volume and regurgitant fraction (as the ratio of forward and backward flow) of pulmonary valve with the scan planes placed appropriately [22]. These images were used to quantify LV and RV volumes, stroke volume (SV), and LV and RV EF. To measure effective SV (EFF SV) regurgitant PV volume was subtracted from SV calculated as the difference between ED and ES RV volumes. All volumes recorded were indexed to BSA.

Statistical Analysis

Normal distribution of data was checked using Shapiro-Wilk test. Data are presented as mean ± standard deviation (SD) for continuous variables or percentages for categorical variables. Echo parameters were acquired at three time points: before the pre-stenting (PRE), immediately after PPVI (POST) and at 3 months follow up (3MFU) while CMR parameters were evaluated in two time points (PRE and 3MFU). Changes of parameters over time were assessed using mixed models with an unstructured covariance matrix and time as a fixed effect with Bonferroni post-hoc correction for multiple comparisons. This type of statistical analysis was chosen over ANOVA for repeated measures to account for missing data in the datasets. Comparison of variables between two time points was performed with paired sample *t*-test. Comparison of categorical variables was assessed by a chi-square test. Reported percentage changes consider the parameters at 3MFU versus PRE.

In order to determine the most potent factors associated with favorable RV reverse remodelling, a multiple linear regression model with RV ΔEDA as dependent variable and time after last surgical intervention, gender, NYHA functional class, $TAPSE_{PRE}$, RV GLS_{PRE}, RV FAC_{PRE} as potential regressors was used. RV ΔEDA was preferred to relative RV volumes' change as variable reflecting RV remodelling, since RV ΔEDA data were available for all study patients, while RV volume data extracted from paired CMR acquisitions existed for 14 patients. Additionally, the variables entering the multiple regression model were selected from a large group of pre-PPVI clinical, RV volumetric and deformation parameters based on the demonstration of statistically significant univariate regressions with RV ΔEDA. Receiver operating characteristic (ROC) curves were used to determine the optimal cut-off for significant regressors coming out from the linear regression models. To characterize patients with best RV reverse remodelling, we compared clinical and imaging variables of those in the upper quartile of RV ΔEDA (RV ΔEDA $< -20\%$ in 3 months) to the rest of the cohort using *t*-test. Intra- and inter- observer variability of measurements is described by the coefficient of variation for the following variables: RVD1, RV EDA, RA AREA and LV end diastolic diameter, RV FAC, TAPSE, and RV-GLS. A two-sided *P*-value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS statistics software (v 20.0, IBM, Chicago, IL).

RESULTS

Demographic Characteristics

Twenty patients with primary surgical correction of ToF and pure PR underwent Melody valve implantation. All were pre-stented. Patient characteristics are reported in Table I. Mean age at surgical intervention for ToF was 1.1 years (range 0.01–12.4 years). Fifteen patients (75%) had received a transannular patch. CMR studies both PRE and 3MFU were available in 14 patients.

TABLE I. Baseline Patient Characteristics along with Pre-stenting and PPVI Procedural Characteristics ($n = 20$)

Demographics	
Age (years)	13.9 ± 9.2 (4.3–44.9)
Gender (male)	14 (70%)
Weight (kg)	43.6 ± 20.7 (16–80)
Height (cm)	146.9 ± 25.1 (107–192)
BSA (m^2)	1.3 ± 0.42 (0.7–2.07)
HR (beats/min)	80.2 ± 11.9
Years after final RVOT Intervention	9.5 ± 4.8 (1.99–32.46)
NYHA Class Pre-Intervention	
I	15 (75%)
II	4 (20%)
III	1 (5%)
Indications for Implantation	
Asymptomatic+ Morphologic criteria (mainly RV dilatation)	17 (85%)
Symptomatic+Exercise Intolerance or Syncope	3 (15%)
Procedural Characteristics	
PR grade	
3+ (Moderate–Severe)	6 (30%)
4+ (Severe)	14 (70%)
RVOT gradient (PRE) (mm Hg)	14.9 ± 6.8
Pre-stent size (length)	
30 mm	1 (5%)
39 mm	10 (50%)
43 mm	8 (40%)
57 mm	1 (5%)
MELODY valve diameter	
20 mm	2 (10%)
22 mm	3 (15%)
24 mm	15 (75%)

BSA: Body Surface Area, HR: Heart Rate, RVOT: Right Ventricular Outflow Tract, NYHA: New York Heart Association, RV: Right Ventricle, PPVI: Percutaneous Pulmonary Valve Implant, PR: Pulmonary Regurgitation, Numbers in brackets correspond to percent over the cohort. Numbers in parentheses correspond to range.

Pre-Stenting and PPVI Procedural Characteristics

The technical details of our protocol are described in Table I. PR was abolished in all patients after PPVI (none or trivial PR) while the RVOT gradient remained unchanged. There was no procedural or peri-procedural complication, coronary artery compromise or death. No major adverse event or relevant valvular dysfunction was recorded during follow up. One patient showed a slight external stent collapse but normal valvular position and function.

Morphological and Functional Alterations after PPVI

Right Bundle Branch Block was the main ECG pattern before and after PPVI (18 patients, 90%), while

TABLE II. Morphological and Functional Characteristics of Cohort Patients, Pre-, Post-Procedure and at 3 Months Follow Up

Variables	PRE-	POST-	3MFU	*P* values
RV Parameters				
RVD1 indexed (mm/m^2)	32.4 ± 9.1	31.1 ± 9.5	29.5 ± 8.8	<0.0005†
RVD2 indexed (mm/m^2)	29.4 ± 6.5	26.9 ± 7.6	25.5 ± 6.1	<0.0005*†
RVD3 indexed (mm/m^2)	56.6 ± 12.4	57.1 ± 12.8	57.2 ± 13.6	0.545
RV EDA indexed (cm^2/m^2)	17.6 ± 2.9	17.4 ± 3.2	15.8 ± 2.7	0.001†
RV ESA indexed (cm^2/m^2)	10.1 ± 2.2	10.9 ± 2.3	9.8 ± 1.7	0.03
RA AREA indexed (cm^2/m^2)	10.5 ± 1.5	10.3 ± 1.9	6.2 ± 1	<0.0005†
RV FAC (%)	0.42 ± 0.08	0.37 ± 0.07	0.37 ± 0.06	0.031
RV TAPSE (mm)	16.8 ± 1.5	15.8 ± 2.2	15.5 ± 2.2	0.055
RV TDI S' (mm)	8.2 ± 1.5	7.2 ± 1.2	7.2 ± 1.2	0.003*†
RV Er (cm/sec)	64.1 ± 14	66.8 ± 13.8	68.3 ± 8.2	0.487
RV Ar (cm/sec)	52.7 ± 17.6	56.2 ± 16	45.5 ± 13.1	0.168
RV Et (cm/sec)	10.5 ± 2.1	8.1 ± 2.6	8.1 ± 2.7	0.008*†
RV E/E'	6.7± 2.4	9.2 ± 3.7	9.5 ± 3.7	0.035*†
LV Parameters				
LVD1 indexed (mm/m^2)	33.6 ± 10.1	32.9 ± 8.2	34.6 ± 8.4	0.389
LVEDD indexed (mm/m^2)	32 ± 8.3	32.9 ± 8.2	34 ± 8.1	<0.0005*†‡
LVESD indexed (mm/m^2)	20.7 ± 5.2	21 ± 6.4	21.7 ± 6.2	0.126
LVEF (%) (ECHO)	58.3 ± 5	59.6 ± 5	60.3 ± 4.7	0.043
LV E (cm/sec)	103.4 ± 18.5	96.9 ± 22.6	60 ± 5.5	<0.0005†
LV A (cm/sec)	41.7 ± 5.8	51 ± 14.1	47.6 ± 10.8	0.121
LV Em(cm/sec)	15.9 ± 2.2	13.8 ± 2.6	12.2 ± 2.8	0.002†
LV E/E'	6.8 ± 1.6	7.3 ± 1.9	8.8 ± 1.5	0.007†
LV TDI S'(cm/sec)	8.7 ± 1.3	8.1 ± 1.2	7.9 ± 2	0.24
RVD1/LVD1	0.98 ± 0.18	0.94 ± 0.13	0.85 ± 0.15	0.024†

PRE: data before procedure, POST: data the day after valve implantation, 3MFU: 3 months follow up, RV: right ventricle, LV: left ventricle, RVD1: basal right ventricular inflow diameter at the tips of the tricuspid valve leaflets, RVD2: right ventricular midventricular short axis diameter, RVD3: right ventricular long axis diameter from right ventricular apex to the level of the tricuspid annulus, RV EDA: right ventricular end-diastolic area, RV ESA: right ventricular end-systolic area, RA AREA: right atrial area, FAC: fractional area change calculated as (RVEDA-RVESA)/RVEDA, RV TAPSE: right ventricular tricuspid annular plane systolic excursion, TDI S': tissue Doppler imaging systolic wave velocity acquired from tricuspid lateral annulus, GLS: global longitudinal strain, LVD1: basal left ventricular inflow diameter at the tips of mitral valve leaflets, LVEDD: left ventricular end diastolic diameter, LVESD: Left ventricular end systolic diameter, LVEF: left ventricular ejection fraction, Er, Ar, E,A, Em, Et: trans-tricuspid (r) and trans-mitral inflow waves and pulsed wave Doppler velocities of the lateral tricuspid (Et) and mitral annuli (Em), LV TDI S': tissue Doppler imaging systolic wave velocity acquired from tricuspid lateral annulus, indexed: over body surface area * PRE vs. POST, $P < 0.05$, †PRE vs. 3MFU, $P < 0.05$, ‡POST vs. 3MFU, $P < 0.05$.

QRS duration increased non-significantly after the procedure (135.6 ± 25.6 msec PRE vs. 148.3 ± 20.4 msec at 3MFU, $P = 0.09$). PPVI caused a significant decrease of RV width (RVD1 and 2) while RV length remained constant (RVD3) (Table II). CMR showed a significant reduction of RV- and an increase of LV-volumes (Table III and Fig. 1). RV EDA (delta −13.1 ± 10.6%), FAC (delta −13.3 ± 21.5%) and TAPSE (delta −12.3 ± 14.8%) were lower after the intervention. Especially concerning RV ΔEDA the distribution of values in our cohort was as follows: median—14.5%, range (0.3% to −29%) with 75th quartile −20% and 25th quartile −2.1%. RV-GLS (−23.5 ± 2.5 PRE to −21 ± 2.5% at 3MFU, $P = 0.003$) decreased (more positive strain values less deformation) while RV stroke volume increased. RV-GLS decrease was mainly driven by the apical segments ($P < 0.0005$) with basal and mid segments remaining stable. Additionally, LV strain was not significantly changed ($P = 0.09$), due to deformation decrease in the septal segments, with, however, enhanced deformation in the rest of LV walls (Table IV). Timing parameters of both ventricles were also non-significantly changed (Table IV).

TABLE III. Cardiovascular Magnetic Resonance Volumetric Data

Variables	PRE-	3MFU	*P* values
RV EDV indexed (mL/m^2)	123.1 ± 24.1	101.5 ± 18.3	0.005
RV ESV indexed (mL/m^2)	55 ± 14.9	50 ± 12.8	0.219
RV EFF SV indexed (mL/m^2)	38.4 ± 9.5	51.4 ± 10.7	0.005
RVEF (%)	55.3 ± 8.1	51 ± 7.1	0.025
LV EDV indexed (mL/m^2)	72.5 ± 11.7	84.1 ± 11.8	0.009
LV ESV indexed (mL/m^2)	30.8 ± 6	33.5 ± 6	0.066
LV SV indexed (cm^2/m^2)	42.8 ± 9.2	50.7 ± 8.1	0.023
LVEF (%)	57.5 ± 4.5	60.3 ± 4.4	0.04
RV/LV EDV	1.71 ± 0.3	1.21 ± 0.14	<0.0005
PR (%)	50 + 5	0.5 ± 1	<0.0005

PRE: data before procedure, 3MFU: 3 months follow up, RV EDV: right ventricular end diastolic volume, RV ESV: right ventricular end systolic volume, RV EFF SV: right ventricular effective stroke volume, RVEF: right ventricular ejection fraction, LV: left ventricular, PR: pulmonary regurgitation: backward flow as percentage of forward flow, indexed: over body surface area.

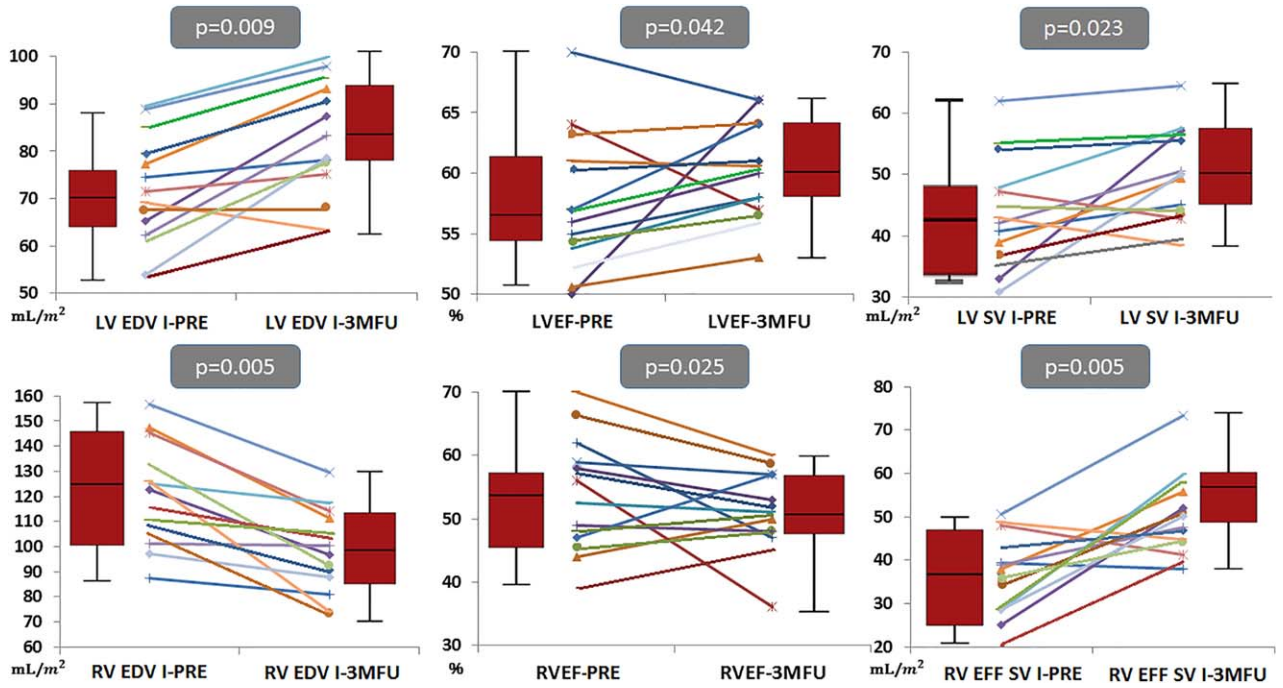

Fig. 1. Line and box plots indicating change in right and left ventricular volumes before (PRE) and 3 months after the intervention (3MFU), as assessed by cardiovascular magnetic resonance imaging. Lines represent individual alterations. RV EDV: right ventricular end diastolic volume, RV ESV: right ventricular end systolic volume, RV EFF SV: right ventricular effective stroke volume, RVEF: right ventricular ejection fraction, LV: left ventricular, I: indexed over body surface area. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE IV. Deformation Imaging Parameters Before and 3 Months after the Implantation of Melody Valve in the Study Population

Strain Variable		PRE	3 MONTHS FU	*P* value
Right Ventricle (RV)				
Free Wall:	Base (%)	−24.5 ± 2.3	−23.5 ± 3.4	0.65
	Mid (%)	−27 ± 4.4	−26.2 ± 5.1	0.43
	Apex (%)	−26.5 ± 3.9	−21.9 ± 2.9	**<0.0005**
Inferoseptal Wall:	Base (%)	−20.4 ± 1.9	−18.6 ± 2.2	0.146
	Mid (%)	−20.6 ± 2.3	−18.5 ± 2.9	0.103
	Apex (%)	−22.1 ± 3	−17.1 ± 2.9	**0.002**
Global RV Strain (%)		−23.5 ± 2.5	−21 ± 2.5	**0.003**
Left Ventricle (LV)				
Anterolateral Wall:	Base (%)	−20.1 ± 5.8	−20.9 ± 9.3	0.75
	Mid (%)	−18.5 ± 3.6	−20.9 ± 4.7	0.08
	Apex (%)	−19.6 ± 3.5	−23.6 ± 3.8	**0.001**
Inferior Wall:	Base (%)	−21 ± 2.1	−21.2 ± 3.6	0.83
	Mid (%)	−21.5 ± 2.4	−23.4 ± 2.7	**0.02**
	Apex (%)	−24.5 ± 3.7	−25.7 ± 4.6	0.37
Anterior Wall:	Base (%)	−18.9 ± 3.9	−21.4 ± 5.2	0.09
	Mid (%)	−24 ± 4.2	−24.4 ± 1.7	0.7
	Apex (%)	−22.8 ± 4.9	−26 ± 3.3	**0.02**
Inferolateral Wall:	Base (%)	−19.4 ± 2.8	−21.3 ± 2.7	**0.03**
	Mid (%)	−19.2 ± 2.3	−20.8 ± 3.2	0.08
	Apex (%)	−22 ± 3.8	−23.7 ± 3.9	0.17
Anteroseptal Wall:	Base (%)	−21.9 ± 3.4	−17.3 ± 2.3	**0.001**
	Mid (%)	−22.6 ± 3.8	−20.2 ± 2.5	**0.02**
	Apex (%)	−24.2 ± 4.3	−23.3 ± 2.6	0.43
Global LV Strain (%)		−20.3 ± 2.3	−21.5 ± 2.1	0.09
Timing Parameters				
RV:	Time to Peak Strain (msec)	453.7 ± 47.1	443.4 ± 53.7	0.52
	Mechanical Dispersion	33.9 ± 10.9	31 ± 15.4	0.5
LV:	Time to Peak Strain (msec)	426.4 ± 42	426.8 ± 35.6	0.97
	Mechanical Dispersion	30.9 ± 13	28 ± 12.7	0.48
Inter-Ventricular Delay (msec)		27 ± 44.6	16.6 ± 44.6	0.47
Pulmonic Valve Closure (msec)		461 ± 34	479 ± 28.2	0.08
Aortic Valve Closure (msec)		425.5 ± 26.5	430.8 ± 19.4	0.47

Calculation of global LV strain was based on the average of 18 segments including the inferoseptal wall presented in RV. Times are corrected for heart rate based on Bazett's formula (Ref. 21). *P* values <0.05 are considered statistically significant have been highlighted in bold.

Three months after MELODY implantation, none of the enrolled patients had reached an indexed RV EDA below the upper limit of the normal reference range.

Time Interval after Last Surgical ToF Repair as a Predictor of RV Remodelling

Potential predictors of reverse RV remodelling after PPVI are shown in Table V. Time after last surgical RVOT correction turned out to be the only significant regressor for RV ΔEDA [$R^2 = 0.60$, beta = 0.387, 95%CI(0.07–0.7), $P = 0.019$] (Fig. 2A and B). By applying ROC curve analysis, setting RV ΔEDA$< -20\%$ as the target classification variable and time interval after last surgical RVOT correction as the examined variable, a cut off of 7 years was depicted [Area under the curve (AUC)=0.725, 95%CI (0.624–0.868), $P = 0.04$ showing a sensitivity of 75% and a specificity of 100%). Characteristics of patients with PPVI after more or less than 7 years are presented in Table VI and Fig. 3. There was no significant difference between the two groups concerning the severity of tricuspid regurgitation or PR. Based on our MRI volumetric data, there was no significant difference in the pulmonary regurgitation fraction (% of

TABLE V. Multiple Regression Analysis with Relative Change in Right Ventricular End Diastolic Area (RV ΔEDA) as Dependent Variable (Model R^2 =0.60)

Variables	Beta (95%CI)	*P* values
Years after final intervention	**0.387 (0.07–0.7)**	**0.019**
Gender (cat.)	2.68 (−0.19–5.6)	0.064
NYHA FC (cat.)	−0.029 (−3.3–3.3)	0.985
TAPSE pre	−0.85 (−1.7–0.037)	0.059
RV GLS pre	0.036 (−0.68–0.75)	0.913
RV FAC pre	−1.5 (−24.2–21.2)	0.886

Cat: Categorical variable, NYHA: New York Heart Association, FC: Functional class, TAPSE: Tricuspid annular plane systolic excursion, pre: Data before procedure, RV: Right ventricle, GLS: Global longitudinal strain, FAC: Fractional area change.
Statistically significant values ($P < 0.05$) have been highlighted in bold.

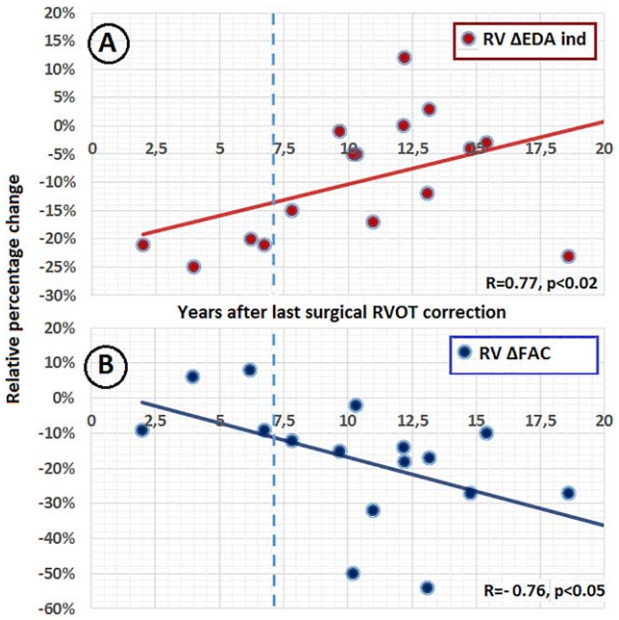

Fig. 2. Dot plots representing percentage change of right ventricular end diastolic area (panel A) and fractional area change (panel B) at 3 months follow in relation with time interval after final right ventricular outflow tract correction. RV ΔEDA ind: Percentage change in right ventricular end diastolic area indexed to body surface area, RV ΔFAC: Percentage change in right ventricular fractional area change, RVOT: Right ventricular outflow tract. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE VI. Patients' Characteristics in Relation to the Time Interval after Final Intervention in RVOT

Variables	<7 Years (*N* = 5)	>7 Years (*N* = 15)	*P* values
Current age (years)	7.7 ± 4.5	16 ± 9.5	0.078
Years after final intervention (years)	4.6 ± 1.9	13.5 ± 5.9	0.004
Gender (Male)	2 (40%)	12 (80%)	0.13
BSA (m^2)	1 ± 0.44	1.4 ± 0.38	0.05
HR pre (beats/min)	91.8 ± 5.8	74.9 ± 10.1	0.004
NYHA FC	I 3(60%)	I 12 (80%)	0.393
	II 2(40%)	II 2 (13.3)	
		III (6.7%)	
PR grade (3+/4+)	3+ 1 (20%)	3+ 5 (33.3%)	0.54
	4+ 4 (80%)	4+ 10 (66.7%)	
RV EDA ind pre (cm^2/m^2)	19.4 ± 2.8	16.9 ± 2.1	0.05
RV FAC pre (%)	0.39 ± 0.02	0.42 ± 0.1	0.425
RV TAPSE pre (mm)	15.8 ± 1.1	16.6 ± 2.1	0.419
RV GLS (%)	−23.8 ± 1.8	−22.8 ± 2.7	0.462
RVD1/LVD1	0.98 ± 0.12	0.98 ± 0.16	0.953

RVOT: Right ventricular outflow tract, BSA: Body surface area, HR: Heart rate, PRE: data before procedure, NYHA FC: New York heart association functional class, PR: Pulmonary regurgitation, RV EDA ind: Right ventricular end diastolic area indexed to BSA, FAC: Fractional area change, TAPSE: Tricuspid annular plane systolic excursion, GLS: Global longitudinal strain, RVD1/LVD1: basal right ventricular inflow diameter at the tips of the tricuspid valve leaflets over basal left ventricular inflow diameter at the tips of mitral valve leaflets.

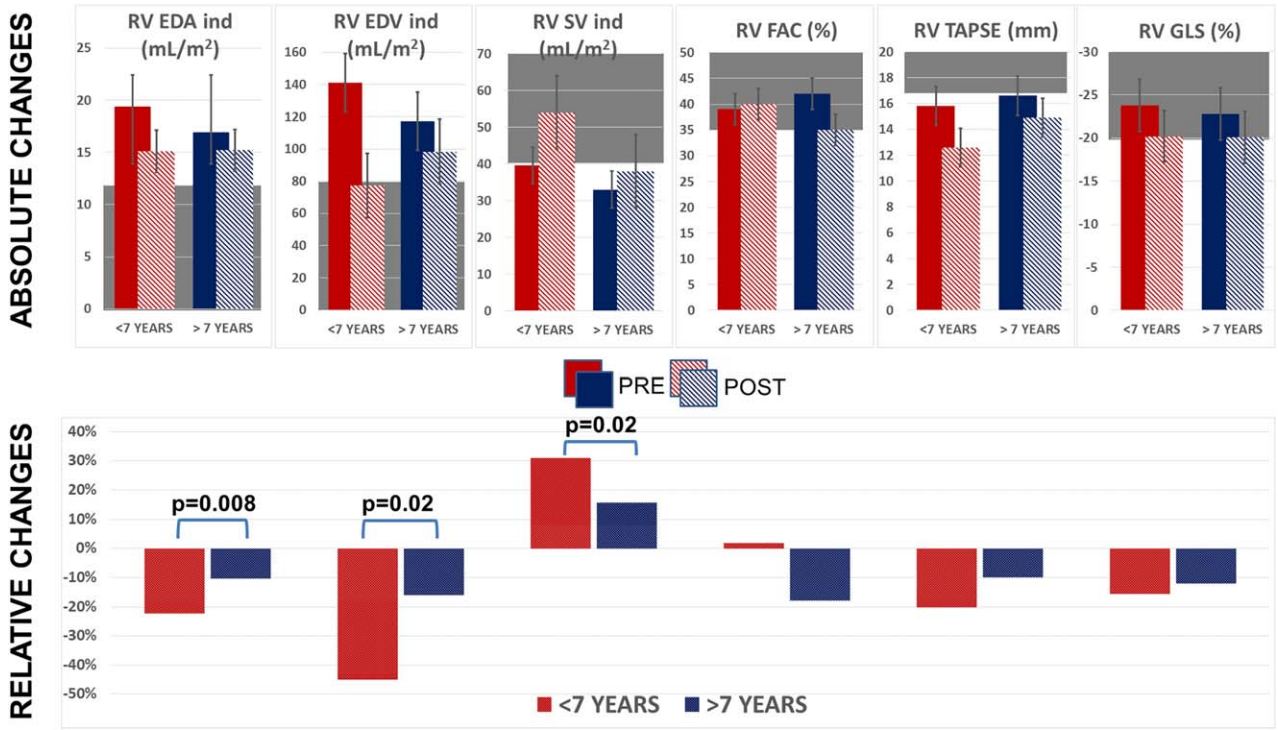

Fig. 3. Bar plots representing absolute (upper panel) and relative (bottom panel) changes in relation with time interval group. Shaded areas in the background represent normal range values as adapted by Ref. 16. RV EDA: Right ventricular end diastolic area assessed by echocardiography, RV EDV: Right ventricular end diastolic volume assessed by cardiovascular magnetic resonance (CMR), RV SV: Right ventricular effective stroke volume assessed by CMR, RV FAC: right ventricular fractional area change, RV TAPSE: Tricuspid annular plane systolic excursion, RV GLS: Global Longitudinal Strain, ind: indexed over body surface area. CMR data based on paired acquisitions come from 4 patients belonging to <7 years group and 10 patient from >7 years group. [Color figure can be viewed at wileyonlinelibrary.com]

backward flow over the forward flow) between the two groups, showing an average value of 50 ± 0.5%

Intra- and Interobserver Variability

For RV structural indices, intra-observer coefficients of variation for RVD1, RV EDA, RA AREA and LV end diastolic diameter were 3%, 4%, 2%, and 2%, respectively, with inter-observer coefficients of variation being 5%, 7%, 5%, and 5%, respectively. Feasibility for 2D RV-GLS analysis of the right ventricle reached 100%. Intra- and inter-observer coefficients of variation for functional indices such as RV FAC, TAPSE, and RV-GLS were 3%, 4%, 8%, and 7%, 5% and 10%, respectively.

DISCUSSION

In a cohort of patients with corrected ToF undergoing PPVI due to severe PR, we have shown that: (i) biventricular reverse remodelling and functional improvement is evident 3 months after the valve implantation and (ii) earlier interventions (<7 years after final RVOT operation) are associated with a more favorable structural and functional improvement with characteristics closer to or within normal range.

RV Remodelling after PPVI

Based on both echocardiographic and CMR data, we found that PPVI in PR patients is followed by a significant reduction in RV dimensions, an increase in SV and concomitantly an improvement in LV volume and output, which is in accordance with previous studies [7,10,23–25]. The advantageous effect of RV unloading has also been reported after other interventions resulting in decrease of RV load such as atrial septal defect closure [26]. The improvement in LV hemodynamics after PPVI could be explained in two ways. First, the elimination of regurgitant fraction leads to an improved RV forward flow, increases LV pre-load and results in higher LV output through a Frank-Starling mechanism [6]. Second, unloading of RV effects, by interventricular interaction via the septum, LV filling [8] allowing through this higher cardiac output.

The significant unloading of the RV after PPVI is not only accompanied by an increase in RV SV, but also with a concomitant reduction of often used echocardiographic surrogate parameters of RV systolic function such as RV FAC, TAPSE, TDI S', and RV-GLS. This underlines once more, that these parameters need to be interpreted in the context of ventricular geometry and loading conditions and do not directly reflect RV myocardial function or even contractility [27–29]. We hypothesize, that the great discrepancy among the results reported by previous studies [8–10,30,31] after PPVI must be explained by the differences in populations enrolled (PR vs. PS and mixed PV pathology) and their variability in RV volumes, geometry and dysfunction. Therefore we believe that our strict focus on a well-defined population of patients with mainly PR allows a better understanding of the underlying pathophysiology of the RV and its alterations after PPVI.

Since none of the non-invasive RV function and dimension parameters fully normalized after PPVI, a follow up of these patients based on imaging indices is challenging. In agreement with previous studies [10], we have shown that RV changes after PPVI are characterized by RV EDV decrease and an increase in effective SV measured by CMR. However, CMR is not always applicable and may suffer from artifacts caused by the "stented" valve [10]. Other approaches, such as cardiopulmonary exercise stress testing [10] might be less feasible in early childhood. Consequently, echocardiography remains the modality of choice for patient follow-up and echo assessment should focus on the relative alteration of RV geometry from pre-interventional values. In our population, patients with the best remodelling (upper quartile) had a RV EDA change of - 20% three months after PPVI. To which extend favorable reverse remodelling translates into better long term outcome, remains to be addressed by further research.

Impact of Timing of PPVI: The Earlier the Better?

Following our cohort of ToF patients with severe secondary PR, we have noted that favorable reverse RV remodelling was more prominent in patients treated less than 7 years after a severe PR was established by a surgical RVOT intervention. In this subgroup of patients, we have also found a "preservation" of RV function and an increase in SV, while in the rest of the cohort the same parameters deteriorated or did not improve.

Timing of PV replacement after RVOT correction in ToF has been a matter of debate over the past few years. The increasing procedural mortality of repeated surgical implantations of bioprosthetic valves with their limited functional life time [9,24], is an obstacle for an optimal timing of surgical PV replacement. Over the past years, the continuous refinement of the PPVI technique which may even allow valve-in-valve implantations, has led to a robust complementary or even alternative method to surgery which adds new aspects to the discussion on optimal timing for PV replacement. The current approach of treating only patients with symptoms or progressive RV remodelling may result in irreversible damage of the RV myocardium [9,10,12,23,32] which may prevent an adequate recovery of its function and a close to normal outcome for the patients [9]. Our study indicates that the total time of exposition to RV volume overload has a significant influence on the magnitude of reverse remodelling, even among asymptomatic patients, suggesting that an earlier intervention (<7 years) might be accompanied by more favorable functional and structural RV recovery. However, whether these short-term observations may be translated into a better long-life outcome (meaning a close to normal life time free of cardiac decompensation) cannot be answered by our current study as it would demand the collection of long-term data (>40 years). Potential complications such as infective endocarditis [9], are also parameters to consider for selecting the optimal time for intervention. Nonetheless, our study is one of the first (based on PPVI approach) to provide evidence in favor of an earlier intervention which may contribute to the continuing discussion about an adequate time point to take action against the deleterious impact of chronic pulmonic regurgitation.

Study Limitations

The size of our cohort was small even though comparable to most of the previous single-center studies in the field. The small number of enrolled patients does not allow the deduction of final conclusions from our findings. On these grounds our study should be considered by its nature as hypothesis generating, triggering further research.

RV ΔEDA, as used to indicate favorable remodeling in our cohort, does not show high correlations with volumetric data. However this parameter was the best among the available ones to describe RV remodelling, since CMR data (before and after) were available in 14 out of 20 patients in our study and all functional parameters decreased after PPVI.

The follow-up interval after PPVI was short. Longer-term and multi-center studies will be needed to confirm our findings, to determine the longevity of percutaneous valves and to investigate the long-term outcome in early treated patients. Additionally, even though evident, the clinical significance of RV systolic parameters' decrease after PPVI has yet to be determined.

Changes in RV and LV volumetrics and function may not translate into improved patients' symptoms, morbidities or sudden death. Although recording of clinical

events was not the scope of this paper, it is expected that real long-term follow up studies will be needed to evidence the clinical impact of PPVI.

Finally, lack of cardiopulmonary exercise test (CPET) data could be considered a limitation of our study, even though performance and interpretation of CPET among pediatric patients is a major challenge.

CONCLUSIONS

In patients with severe PR secondary to a surgical correction of ToF biventricular reverse remodelling is evident as early as 3 months after PPVI. Earlier interventions (<7 years after last surgical RVOT correction) are associated with more pronounced reverse remodelling leading to close to or even normal RV dimensions and function. Our data provide evidence that earlier interventions using stented valves may be beneficial for the patient and may have direct impact on current guidelines for the clinical management of ToF patients.

REFERENCES

1. Geva T. Tetralogy of Fallot repair: Ready for a new paradigm. J Thorac Cardiovasc Surg 2012;143:1305–1306.
2. Cuypers JA, Menting ME, Konings EE, Opić P, Utens EM, Helbing WA, Witsenburg M, van den Bosch AE, Ouhlous M, van Domburg RT, Rizopoulos D, Meijboom FJ, Boersma E, Bogers AJ, Roos-Hesselink JW. Unnatural history of tetralogy of Fallot: Prospective follow-up of 40 years after surgical correction. Circulation 2014;130:1944–1953.
3. Gatzoulis MA, Till JA, Somerville J, Redington AN. Mechanoelectrical interaction in tetralogy of Fallot. QRS prolongation relates to right ventricular size and predicts malignant ventricular arrhythmias and sudden death. Circulation 1995;92:231–237.
4. Hickey EJ, Veldtman G, Bradley TJ, Gengsakul A, Manlhiot C, Williams WG, Webb GD, McCrindle BW. Late risk of outcomes for adults with repaired tetralogy of Fallot from an inception cohort spanning four decades. Eur J Cardiothorac Surg 2009;35: 156–164.
5. Cools B, Brown SC, Heying R, Jansen K, Boshoff DE, Budts W, Gewillig M. Percutaneous pulmonary valve implantation for free pulmonary regurgitation following conduit-free surgery of the right ventricular outflow tract. Int J Cardiol 2015;186:129–135.
6. Harrild DM, Marcus E, Hasan B, Alexander ME, Powell AJ, Geva T, McElhinney DB. Impact of transcatheter pulmonary valve replacement on biventricular strain and synchrony assessed by cardiac magnetic resonance feature tracking. Circ Cardiovasc Interv 2013;6:680–687.
7. Cheatham JP, Hellenbrand WE, Zahn EM, Jones TK, Berman DP, Vincent JA, McElhinney DB. Clinical and hemodynamic outcomes up to 7 years after transcatheter pulmonary valve replacement in the US melody valve investigational device exemption trial. Circulation 2015;131:1960–1970.
8. Chowdhury SM, Hijazi ZM, Rhodes JF, Kar S, Makkar R, Mullen M, Cao QL, Mandinov L, Buckley J, Pietris NP, Shirali GS. Changes in speckle tracking echocardiography measures of ventricular function after percutaneous implantation of the Edwards SAPIEN transcatheter heart valve in the pulmonary position. Echocardiography 2015;32:461–469.
9. Geva T. Indications for pulmonary valve replacement in repaired tetralogy of Fallot: The quest continues. Circulation 2013;128:1855–1857.
10. Vezmar M, Chaturvedi R, Lee KJ, Almeida C, Manlhiot C, McCrindle BW, Horlick EM, Benson LN. Percutaneous pulmonary valve implantation in the young 2-year follow-up. J Am Coll Cardiol Intv 2010;3:439–448.
11. Boshoff DE, Cools BL, Heying R, Troost E, Kefer J, Budts W, Gewillig M. Off-label use of percutaneous pulmonary valved stents in the right ventricular outflow tract: Time to rewrite the label? Catheter Cardiovasc Interv 2013;81:987–995.
12. Babu-Narayan SV, Kilner PJ, Li W, Moon JC, Goktekin O, Davlouros PA, Khan M, Ho SY, Pennell DJ, Gatzoulis MA. Ventricular fibrosis suggested by cardiovascular magnetic resonance in adults with repaired tetralogy of Fallot and its relationship to adverse markers of clinical outcome. Circulation 2006; 113:405–413.
13. Khambadkone S, Coats L, Taylor A, Boudjemline Y, Derrick G, Tsang V, Cooper J, Muthurangu V, Hegde SR, Razavi RS, Pellerin D, Deanfield J, Bonhoeffer P. Percutaneous pulmonary valve implantation in humans. Results in 59 consecutive patients. Circulation 2005;112:1189–1197.
14. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2015;16:233–271.
15. DuBois D, DuBois EF. A formula to estimate the approximate surface area if height and weight be known. Arch Intern Med 1916;17:863–871.
16. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, Solomon SD, Louie EK, Schiller NB. Guidelines for the echocardiographic assessment of the right heart in adults: A report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr 2010;23:685–713.
17. Horton KD, Meece RW, Hill JC. Assessment of the right ventricle by echocardiography: A primer for cardiac sonographers. J Am Soc Echocardiogr 2009;22:776–792.
18. Pagourelias ED, Kouidi E, Efthimiadis GK, Deligiannis A, Geleris P, Vassilikos V. Right atrial and ventricular adaptations to training in male Caucasian athletes: An echocardiographic study. J Am Soc Echocardiogr 2013;26:1344–1352.
19. Van De Bruaene A, De Meester P, Voigt JU, Delcroix M, Pasquet A, De Backer J, De Pauw M, Naeije R, Vachiéry JL, Paelinck B, Morissens M, Budts W. Right ventricular function in patients with Eisenmenger syndrome. Am J Cardiol 2012; 109:1206–1211.
20. Voigt JU, Pedrizzetti G, Lysyansky P, Marwick TH, Houle H, Baumann R, Pedri S, Ito Y, Abe Y, Metz S, Song JH, Hamilton J, Sengupta PP, Kolias TJ, d'Hooge J, Aurigemma GP, Thomas JD, Badano LP. Definitions for a common standard for 2D speckle tracking echocardiography: Consensus document of the EACVI/ASE/industry task force to standardize deformation imaging. J Am Soc Echocardiogr 2015;28:183–193.
21. Bazett HC. An analysis of the time-relations of electrocardiography. Heart 1920;7:353–370.
22. Myerson SG. Heart valve disease: Investigation by cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2012;14:17.

23. Frigiola A, Tsang V, Bull C, Coats L, Khambadkone S, Derrick G, Mist B, Walker F, van Doorn C, Bonhoeffer P, Taylor AM. Biventricular response after pulmonary valve replacement for right ventricular outflow tract dysfunction: Is age a predictor of outcome? Circulation 2008;118:S182–S190.
24. Geva T. Repaired tetralogy of Fallot: The roles of cardiovascular magnetic resonance in evaluating pathophysiology and for pulmonary valve replacement decision support. J Cardiovasc Magn Reson 2011;13:9.
25. Geva T, Gauvreau K, Powell AJ, Cecchin F, Rhodes J, Geva J, del Nido P. Randomized trial of pulmonary valve replacement with and without right ventricular remodelling surgery. Circulation 2010;122:S201–S208.
26. Bussadori C, Oliveira P, Arcidiacono C, Saracino A, Nicolosi E, Negura D, Piazza L, Micheletti A, Chessa M, Butera G, Dua JS, Carminati M. Right and left ventricular strain and strain rate in young adults before and after percutaneous atrial septal defect closure. Echocardiography 2011;28:730–737.
27. Savu O, Jurcuţ R, Giuşcă S, van Mieghem T, Gussi I, Popescu BA, Ginghină C, Rademakers F, Deprest J, Voigt JU. Morphological and functional adaptation of the maternal heart during pregnancy. Circ Cardiovasc Imag 2012;5:289–297.
28. Bijnens BH, Cikes M, Claus P, Sutherland GR. Velocity and deformation imaging for the assessment of myocardial dysfunction. Eur J Echocardiogr 2009;10:216– 226.
29. Giusca S, Dambrauskaite V, Scheurwegs C, D'hooge J, Claus P, Herbots L, Magro M, Rademakers F, Meyns B, Delcroix M, Voigt JU. Deformation imaging describes right ventricular function better than longitudinal displacement of the tricuspid ring. Heart 2010;96:281–288.
30. Lurz P, Coats L, Khambadkone S, Nordmeyer J, Boudjemline Y, Schievano S, Muthurangu V, Lee TY, Parenzan G, Derrick G, Cullen S, Walker F, Tsang V, Deanfield J, Taylor AM, Bonhoeffer P. Percutaneous pulmonary valve implantation: Impact of evolving technology and learning curve on clinical outcome. Circulation 2008;117:1964–1972.
31. Hughes M, Jones R, Mist B, Pellerin D, Marek J, Deanfield JE, Bonhoeffer P, Taylor AM. Physiological consequences of percutaneous pulmonary valve implantation: The different behavior of volume- and pressure-overloaded ventricles. Eur Heart J 2007; 28:1886–1893.
32. Borik S, Crean A, Horlick E, Osten M, Lee KJ, Chaturvedi R, Friedberg MK, McCrindle BW, Manlhiot C, Benson L. Percutaneous pulmonary valve implantation: 5 years of follow-up: Does age influence outcomes? Circ Cardiovasc Interv 2015;8:e001745.33